INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/37291

A.	CLASSIFICATION OF SUBJECT MATTER
IPC(7)	: G06F 19/00
US CL	: 702/27

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/4,6; 702/19, 20, 22, 27

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Please See Continuation Sheet

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST/WEST, STN, Medline, Biosis, CAPlus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAMURA et al. Sequence and Structural Conservation in RNA Ribose Zippers. Journal of Molecular Biology. 2002, Vol. 320, pages 455-474, see especially Abstract, Figures 8 and 9, Table 2, page 467, column 1, line 10 through column 2, line 41, and page 472, column 2, line 34 through page 437, column 1, line 24.	1, 2, 9, and 10
Y	FRANCH et al. Antisense RNA Regulation in Prokaryotes: Rapid RNA/RNA interaction Facilitated by a General U-turn Loop Structure. Journal of Molecular Biology. 1999, Vol. 294, pages 1115-1125, see especially Abstract, Figures 1 and 3, and page 1115, column 1, line 1 through page 1117, column 2, line 18.	1, 2, 9, and 10
Y	US 6,178,384 B1 (KOLOSSVARY) 23 January 2001 (23.01.2001), see especially Abstract, Figures 2-8, column 4, lines 5-35, and column 4, line 65 through column 12, line 20.	1, 2, 9, and 10
Y	US 6,188,965 B1 (MAYO et al.) 13 February 2001 (13.02.2001), see especially Abstract, Figures 1-4, column 2, lines 15-55, and column 4, line 30 through column 27, line 10.	1, 2, 9, and 10

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent published on or after the international filing date		
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2005 (30.06.2005)	**18 JUL 2005**
Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US	Eric S. DeJong
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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/37291

| Box No. II | Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet) |

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

| Box No. III | Observations where unity of invention is lacking (Continuation of item 3 of first sheet) |

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1,2,9 and 10

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(2)) (January 2004)

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Search Authority has found 4 inventions claimed in the International Application covered by the claims indicated below:

Group I, claims 1, 2, 9 and 10, drawn to systems for generating and refining nucleic acid structures comprising the steps of aligning a reference sequence, making substitutions, deletions, and insertions, identifying conserved hydrogen bonds, and optimizing said structures by use of a force field algorithm.

Group II, claims 3 and 4, drawn to a system for predicting nucleic acid three-dimensional structure comprising the steps of computing and decomposing a plurality of structures, ranking structure motifs, identifying and linking three-dimensional candidates and refining structures using an energy minimization algorithm.

Group III, claims 5 and 6, drawn to a system for generating a nucleic acid structure motif database comprising a step that includes associating data on structural motif, size, backbone coordinates and dihedral angles.

Group IV, claims 7 and 8, drawn to a system for refining nucleic acid structure predictions comprising a step which includes experimental constraints.

This International Search Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2, and 13.3) for the reasons indicated below:

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The common concept between the inventions of Groups I-IV is computational modeling of nucleic acid three-dimensional structures and is already well known in the art. Therefore the special technical feature linking the inventions of Groups I-IV does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of Group I is considered to be a system for three-dimensional modeling of nucleic acids comprising a processor configured to generate an initial uncorrected model of a test sequence by comparison to a reference sequence, aligning secondary structure constraints of a reference structure with a test sequence to generate an aligned sequence, making substitutions, deletions, and insertions dictated by said aligned sequence using geometrical algorithms for said substitutions and using molecular mechanics and molecular dynamics to close gaps caused by said deletions and insertions, identifying conserved hydrogen bonds present in both said reference sequence and said uncorrected model to select hydrogen bond constraints and optimizing said uncorrected model using a force field algorithm that accounts for said hydrogen bond constraints to generate a three-dimensional structure.

The special technical feature of Group II is considered to be a system for predicting nucleic acid three-dimensional structure comprising a processor configured to compute a plurality of secondary structures of a test nucleic acid, decomposing said secondary structures into nucleic acid structure motifs, ranking said structure motifs in a hierarchal tree, identifying candidate three-dimensional structures in an

order specified by said hierarchical tree to generate a candidate three-dimensional composite structure, ranking said one or more refined candidate three-dimensional structures based on the calculated total energy and optionally one or more scoring parameters, and selecting a refined candidate three-dimensional structure based on best calculated energy to predict a three-dimensional structure of said test nucleic acid.

The special technical feature of Group III is considered to be a system for generating a nucleic acid structure database comprising a processor configured to receive nucleic acid physical structure information, decomposing said physical structure information into nucleic acid structure motifs, associating data with said structure motifs, comparing said nucleic acid structure motifs to existing motifs, and adding said structure motif and associated data to said database.

The special technical feature of Group IV is considered to be a system for refining nucleic acid structure predictions comprising a processor configured to calculate energy minimization terms for a test nucleic acid structure prediction model, optimizing force constraints, distance dependence, partial charges, and van der Waals radii parameters, accounting for gap penalties for insertions or deletions and for one or more experimental constraints associated with said test nucleic acid sequence, employing distance constraints within a defined distance range but ignore distance constraints outside said defined distance range, accounting for one or more nucleic acid folding thermodynamic measures, and accounting for known interactions.

Continuation of B. FIELDS SEARCHED Item 2:
Search Terms: three-dimensional, 3D, structure refinement, model(ing), nucleic acid, hydrogen bond, force field, NMR, X-ray, crystallography, alignement, secondary structure.